


# Coagulation and Inflammatory Indicators in Pneumonia Patients with Venous Thromboembolism: A Propensity-Score Matching Study

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**Background:** Venous thromboembolism (VTE) is associated with high morbidity and mortality. In recent years, increasing evidence has suggested that inflammation plays a critical role in the pathogenesis of VTE. Patients with pneumonia often exhibit an inflammatory response. This study aimed to investigate the correlation between inflammatory indicators and VTE by analyzing laboratory indicators in patients with pneumonia and VTE.

**Methods:** Samples were collected from patients with pneumonia admitted between December 2022 and March 2023. Patients were classified into the VTE and non-VTE groups according to whether they had VTE or not. Propensity score matching (PSM) was performed to control for potential confounding factors. Coagulation and inflammatory indicators were measured. Statistical analyses were performed to identify biomarkers that exhibited significant differences between the two groups, and the relationship between coagulation and inflammatory indicators was further explored.

**Results:** D-dimer, thrombin-antithrombin complex (TAT), plasmin- $\alpha$ 2-antiplasmin complex (PIC), t-PA:PAI-1 complex (tPAIC), and thrombomodulin (TM) levels were significantly higher in the VTE group. White blood cell count (WBC), neutrophil-to-lymphocyte ratio (NLR), procalcitonin (PCT), and C-reactive protein (CRP) levels were significantly elevated in VTE group. The areas under the curve (AUC) of the receiver operator characteristic (ROC) curves for D-dimer, TAT, PIC, tPAIC, and TM were 0.806, 0.691, 0.656, 0.621, and 0.641, respectively, while the areas for WBC, NLR, CRP, and PCT were 0.690, 0.647, 0.618, and 0.651, respectively. Correlation analysis revealed that WBC was significantly correlated with D-dimer, TAT, PIC and TM. NLR was correlated with D-dimer and TM. CRP was correlated with D-dimer and TM.

**Conclusion:** There is a significant activation of both coagulation and fibrinolytic systems in pneumonia patients. VTE in pneumonia patients is associated with the activation of inflammatory system. Monitoring inflammatory and coagulation indicators in pneumonia patients can facilitate early identification of individuals at an elevated risk of VTE.

**Keywords:** pneumonia, coagulation, inflammation, indicators

## Introduction

Since COVID-19, it has been recognized that the incidence of Venous thromboembolism (VTE) in pneumonia patients is quite high and pneumonia patients with VTE are associated with worsening disease severity and poorer clinical outcomes.<sup>1,2</sup> However, thrombotic events can be difficult to detect and treat at early stage for the presentation of VTE may be vague and non-specific. In particular, the clinical features of both pulmonary embolism and pneumonia considerably overlap. Imaging examination can only play a role when a clot has already formed; thus, microvascular thrombosis and prethrombotic stage cannot be detected. Therefore, it can be useful to identify blood-based biomarkers

that enable early identification of VTE in patients with pneumonia.<sup>3,4</sup> Besides advanced age and immobilization, pneumonia itself is an independent risk factor for VTE in pneumonia patients.<sup>5</sup> Possibly because pathogens cause local or systemic inflammatory reactions that affect the function of endothelial cells and lead to vascular damage, and coagulation factors are activated. Molecular markers of coagulation and fibrinolysis contribute to the diagnosis of VTE. The use of electrochemiluminescence to detect thrombin-antithrombin complex (TAT), plasmin- $\alpha$ 2-antiplasmin complex (PIC), t-PA:PAI-1 complex (tPAIC), and thrombomodulin (TM) is a technological innovation and breakthrough compared to traditional coagulometric methods. There are few studies evaluating these indicators in pneumonia patients, and our study also focused on these novel coagulation markers.

Some inflammatory markers might be regarded as risk factors for VTE.<sup>6–8</sup> We explored the value and correlation of inflammatory indicators and coagulation indicators in the diagnosis of VTE in pneumonia patients. Propensity score matching (PSM) was performed to control for confounding biases.

## Methods

### Patients Selection

We identified patients with pneumonia at the Henan Provincial People's Hospital between December 2022 and March 2023. The inclusion criteria were as follows: (1) pneumonia diagnosed according to the guidelines of the Infectious Diseases Society of America/American Thoracic Society;<sup>9</sup> (2) age > 18 years. The exclusion criteria were as follows: (1) patients with inherited or acquired coagulation disorders, such as hemophilia, pregnant women, and fractures; and (2) patients on long-term use of anticoagulants. Venous blood samples and demographic data were collected from the patients at admission. Patients with VTE related clinical manifestations and confirmed by imaging examinations during hospitalization were divided into the VTE group, while patients without VTE were divided into non-VTE group. The diagnosis of VTE was confirmed according to the guidelines of chest.<sup>10</sup> The study complied with the Declaration of Helsinki and was approved by the Research Ethics Committee of Henan Provincial People's Hospital.

### Specimen Collection and Measurements

Peripheral blood samples were collected from all the participants. Blood samples for complete blood counts were analyzed using Sysmex XN9100 (Sysmex Corporation, Japan). Albumin (Alb), total protein (TP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), creatine kinase (CK), creatine kinase-MB (CK-MB), and creatinine levels were measured using an Abbott C16000 (Abbott Corporation, USA). C-reactive protein (CRP) levels were determined using Lifotronic PA-990PRO (Shenzhen Lifotronic Technology Corporation, China). Procalcitonin (PCT) was assessed using VIDAS30 (BioMérieux Corporation, France). Routine coagulation indicators, including prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (Fib), D-dimer, and antithrombin (AT), were performed using a Sysmex CS 5100 coagulation analyzer (Sysmex Corporation, Japan). Novel coagulation indicators, including thrombin-antithrombin complex (TAT), plasmin- $\alpha$ 2-antiplasmin complex (PIC), t-PA:PAI-1 complexes (tPAIC), and thrombomodulin (TM), were detected using Sysmex HISCL-5000, a coagulation analyzer based chemiluminescent method (Sysmex Corporation, Japan).

### Statistical Analysis

To mitigate baseline differences, 1:3 propensity score matching (PSM) was performed between the VTE and non-VTE groups based on the following baseline characteristics: age, sex, hypertension, diabetes mellitus, liver disease, kidney disease, heart disease, and malignancy. The Kolmogorov–Smirnov test was used to determine whether continuous variables had a normal distribution. Normally distributed data were expressed as the mean  $\pm$  standard deviation, and two independent samples *t*-test was used for statistical analysis, with a *P* value < 0.05 were considered statistically significant. Non-normally distributed data were reported as medians (interquartile range) and compared using the Mann–Whitney test. Categorical variables were described as counts and percentages and were compared using the chi-squared test. The diagnostic value of the indicators was evaluated using receiver operating characteristic (ROC) curves, and the

area under the curve (AUC) was calculated for different indicators. SPSS version 26.0, R with the MatchIt package (version 4.4.1), and GraphPad Prism version 9.0 were applied for statistical analysis.

## Results

### PSM and Clinical Characteristics

A total of 232 patients met the inclusion criteria and 44 were diagnosed with VTE. After PSM, 42 and 104 patients were enrolled in the VTE and non-VTE groups, respectively, and all baseline confounding features were well-balanced between the two groups (all  $P>0.05$ ). The baseline clinical characteristics before and after PSM are shown in Table 1. The outcomes of the matched patients during their hospital stays are shown in Table 2. Patients with VTE had longer hospital stays and higher mortality rates than those without VTE. Patients with VTE are more likely to develop sepsis and require extracorporeal membrane oxygenation (ECMO). The incidences of severe pneumonia and respiratory failure were also higher in the VTE group than that in the non-VTE group.

### Comparison of Laboratory Analysis Indicators

Among all the laboratory indicators tested in this study, some indicators of coagulation and inflammation differed between the VTE and non-VTE groups. Only D-dimer levels showed differences, whereas PT, APTT, fibrinogen, and AT levels showed no differences in routine coagulation indicators. However, all novel coagulation indicators, including TAT, PIC, tPAIC, and TM, differed between the two groups. In addition, we found that some inflammatory indicators differed (Table 3). There were no differences in the indicators of liver and kidney function. The distribution of coagulation and inflammatory indicators with differences is shown in Figures 1 and 2.

**Table 1** Baseline Clinical Characteristics of Patients Before and After PSM

Variables	Before PSM			After PSM		
	VTE n=44	Non-VTE n=188	P value	VTE n=42	Non-VTE n=104	P value
Age, mean $\pm$ SD	72.64 $\pm$ 7.57	67.75 $\pm$ 16.30	0.136	72.74 $\pm$ 9.77	72.79 $\pm$ 12.69	0.890
Male/Female, n	31/13	133/55	0.970	30/12	76/28	0.840
Hypertension, n (%)	18 (40.91)	85 (45.21)	0.605	18 (42.86)	42 (40.38)	0.783
Diabetes mellitus, n (%)	15 (34.09)	63 (33.51)	0.942	14 (33.33)	31 (29.81)	0.676
Liver disease, n (%)	18 (40.91)	37 (19.68)	0.003*	16 (38.10)	29 (27.88)	0.226
Kidney disease, n (%)	16 (36.36)	46 (24.47)	0.108	14 (33.33)	32 (30.77)	0.763
Heart disease, n (%)	25 (56.82)	79 (42.02)	0.076	23 (54.76)	53 (50.96)	0.677
Malignancy, n (%)	6 (13.64)	20 (10.64)	0.763	6 (14.29)	15 (14.42)	0.983

Note: \* $P<0.05$ .

**Table 2** Complication and Outcomes During Hospitalization

	VTE n=42	Non-VTE n=104	P value
Length of stay, median (Q1, Q3)	25.0 (12.0, 33.5)	14.0 (10.0, 24.0)	0.025*
Severe pneumonia, n (%)	34 (81.0%)	46 (44.2%)	<0.001*
Sepsis, n (%)	18 (42.9%)	12 (11.5%)	<0.001*
Death, n (%)	6 (14.3%)	4 (3.8%)	0.034*
ECMO, n (%)	5 (11.9%)	3 (2.9%)	0.044*
Respiratory failure, n (%)	29 (69.0%)	30 (28.8%)	<0.001*

Note: \* $P<0.05$ .

**Table 3** Laboratory Indicators in VTE and Non-VTE Group

	VTE n=42	Non-VTE n=104	Reference Range	P value
WBC, $\times 10^9$ /L	12.84 $\pm$ 3.63	9.12 $\pm$ 5.68	3.5–9.5	0.002*
%Neut, %	83.69 $\pm$ 7.52	78.39 $\pm$ 15.47	40–75	0.010*
%Lymph, %	6.40 (3.70, 11.65)	9.0 (5.0, 19.10)	20–50	0.002*
NLR	13.17 (7.31, 25.54)	9.41 (3.55, 18.10)	–	0.005*
RBC, $\times 10^{12}$ /L	3.81 $\pm$ 0.59	3.62 $\pm$ 0.77	4.3–5.8	0.367
PLT, $\times 10^9$ /L	271.0 $\pm$ 133.07	204.36 $\pm$ 97.21	125–350	0.388
Alb, g/L	29.75 $\pm$ 4.50	31.94 $\pm$ 4.87	40–55	0.215
TP, g/L	59.30 (53.40, 64.40)	60.0 (55.98, 64.48)	65–85	0.994
ALT, U/L	25.0 (14.50, 46.0)	22.50 (14.78, 43.95)	7–40	0.527
AST, U/L	26.40 (16.80, 38.60)	26.15 (16.70, 33.68)	13–35	0.704
TBIL, $\mu$ mol/L	9.30 (6.50, 12.60)	9.20 (6.75, 12.38)	5–21	0.794
CK, U/L	43.0 (29.0, 140.40)	47.35 (29.18, 75.08)	40–200	0.373
CK-MB, U/L	11.0 (7.0, 16.5)	13.55 (9.03, 17.85)	0–25	0.199
Crea, $\mu$ mol/L	61.0 (50.0, 95.0)	63.5 (50.0, 79.75)	44–104	0.548
CRP, mg/L	79.80 (59.72, 138.52)	22.90 (2.52, 94.25)	0–10	0.026*
PCT, ng/mL	1.05 (0.12, 4.04)	0.05 (0.05, 0.93)	0–0.05	0.003*
PT, S	13.29 $\pm$ 1.14	12.67 $\pm$ 1.03	9–14	0.927
APTT, S	27.2 (25.0, 28.80)	29.9 (27.45, 31.40)	22–32.5	0.118
Fib, g/L	5.02 $\pm$ 1.51	4.10 $\pm$ 1.96	1.8–3.5	0.973
D-dimer, $\mu$ g/mL	4.28 (1.29, 8.0)	0.96 (0.45, 1.89)	0–0.55	<0.001*
ATIII, %	74.30 (66.60, 76.20)	66.70 (61.0, 75.0)	80–130	0.692
TAT, ng/mL	8.65 (3.08, 21.20)	6.50 (3.20, 12.20)	<4.0	<0.001*
PIC, $\mu$ g/mL	1.10 (0.67, 2.08)	0.84 (0.67, 1.08)	<0.8	0.005*
tPAIC, ng/mL	25.10 (16.33, 36.63)	16.50 (10.30, 33.40)	Male: 6.2–14.0 Female: 3.7–9.3	0.040*
TM, TU/mL	15.40 (12.70, 34.40)	11.90 (9.15, 16.73)	3.8–13.3	0.007*

Note: \* $P < 0.05$ .

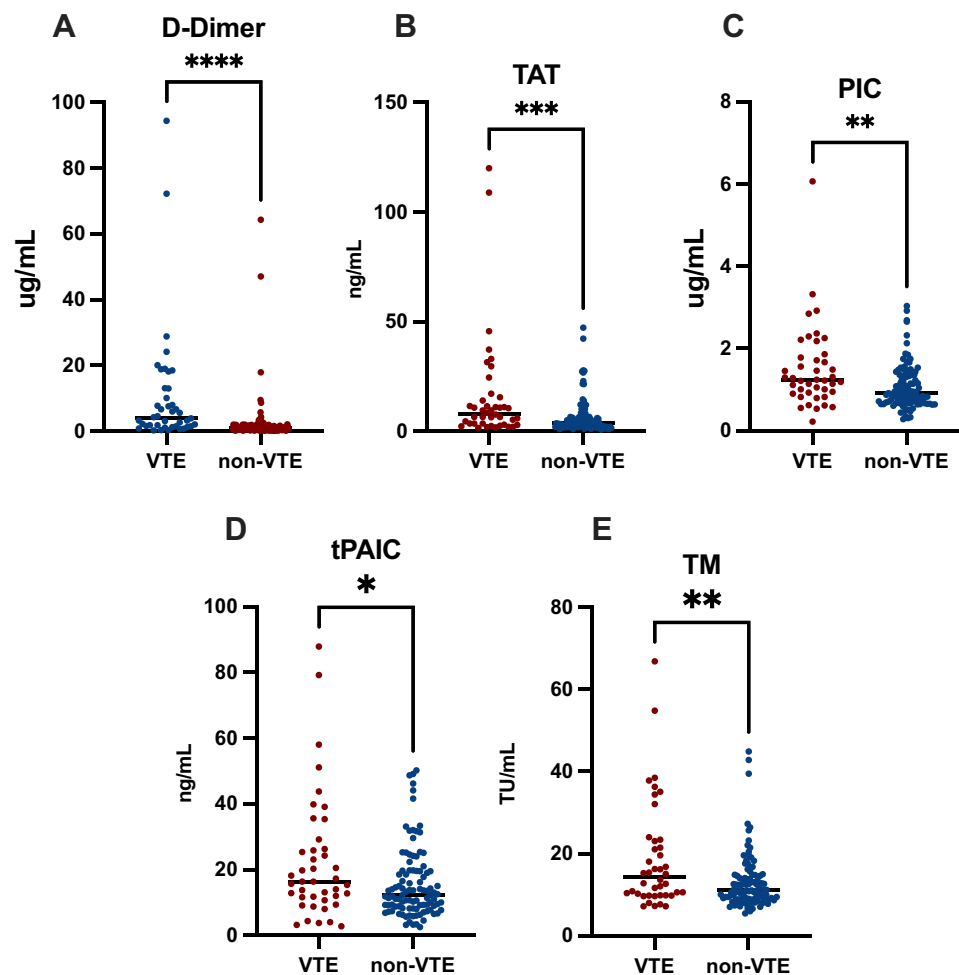
## Evaluation the Correlation of Coagulation and Inflammatory Indicators

The ROC curves are shown in Figure 3. The AUC for D-dimer, TAT, PIC, tPAIC, and TM levels were 0.806, 0.691, 0.656, 0.621, and 0.641, respectively. The AUC for WBC, NLR, CRP and PCT were 0.690, 0.647, 0.618 and 0.651, respectively. We also analyzed the correlation between coagulation and inflammatory indicators. Correlation analysis showed that WBC was correlated with D-dimer, TAT, PIC and TM. NLR was correlated with D-dimer and TM. CRP was correlated with D-dimer and TM ( $P < 0.05$ , Table 4).

## Discussion

As this study aimed to explore VTE-specific markers, potential patient selection bias was excluded. Given that advanced age, cancer, and other comorbidities are risk factors for VTE, and that there are sex differences in the reference range of some indicators, PSM was performed based on age, sex, and common comorbidities.<sup>11,12</sup> No significant differences were found between the groups across all measured baseline characteristics after PSM.

VTE remains a challenge and is a significant cause of patient mortality worldwide.<sup>13</sup> In our study, VTE events were significantly associated with increased mortality and length of stay. The proportion of sepsis in VTE group is higher than that in non-VTE group which may be due to that the systemic inflammatory milieu of sepsis may uniquely predispose patients to VTE.<sup>14</sup> In the non-VTE group, the median levels of coagulation indicators, such as D-dimer, TAT, PIC and tPAIC, were found to be elevated above the upper reference range. This suggests widespread activation of both the coagulation and fibrinolytic systems in patients with pneumonia independent of VTE.



**Figure 1** Comparison of coagulation indicators.

**Notes:** (A) Differences in D-dimer distribution between VTE and non-VTE groups; (B) Differences in TAT distribution between VTE and non-VTE groups; (C) Differences in PIC distribution between VTE and non-VTE groups; (D) Differences in tPAIC distribution between VTE and non-VTE groups. (E) Differences in TM distribution between VTE and non-VTE groups. \*indicates  $P < 0.05$ ; \*\*indicates  $P < 0.01$ ; \*\*\*indicates  $P < 0.001$ ; \*\*\*\*indicates  $P < 0.0001$ .

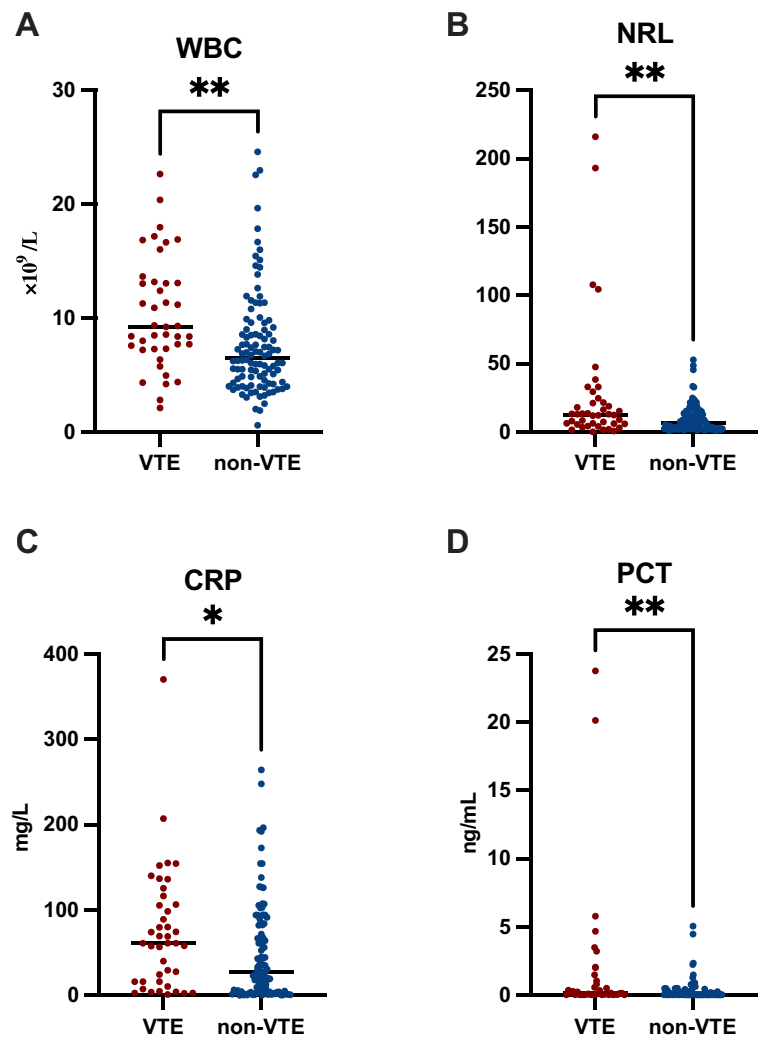
White blood cells can cause blood clots to adhere to the vessel wall.<sup>15</sup> Leukocytosis was found to be associated with an increased risk of VTE and mortality in cancer patients receiving systemic chemotherapy.<sup>16</sup> Similar characteristics were also observed in pneumonia patients in our study.

Neutrophilia is a well-known independent risk factor of VTE. Neutrophil extracellular traps (NETs) activate the intrinsic coagulation pathway by directly activating factor XII (FXII), binding to von Willebrand factor (vWF) and triggering platelet recruitment. In addition, neutrophil-derived enzymes have been found to inhibit anticoagulant factors such as tissue factor pathway inhibitors, antithrombin and protein C.<sup>17</sup>

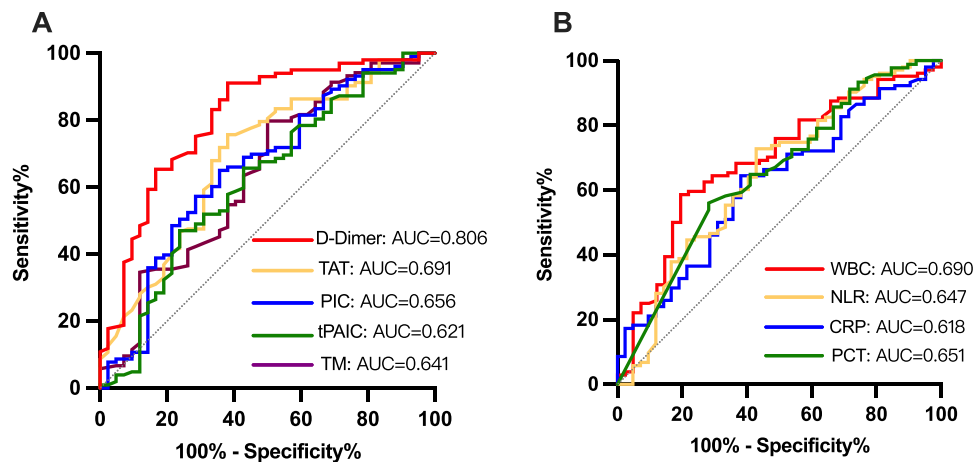
However, the level of lymphocytes is always restrained with thrombus formation, although the mechanisms remain unclear.<sup>6</sup> Previous studies have revealed that T cell senescence and dysfunction show a remarkably higher risk of progressive thrombosis and abnormal coagulation in COVID-19.<sup>18</sup>

We observed neutrophilia and lymphopenia in patients with VTE; therefore, the neutrophil/lymphocyte ratio (NLR) may be a useful indicator that can be easily calculated from the results of complete blood cell count.

PCT and CRP are acute phase reaction proteins. CRP can directly affect the endothelial phenotype and promote platelet adhesion to endothelial cells.<sup>19</sup> Previous studies have indicated that CRP  $> 3\text{ug/mL}$  may predict the occurrence of VTE in the future.<sup>20</sup>



**Figure 2** Comparison of inflammatory indicators. **Notes:** (A) Differences in WBC distribution between VTE and non-VTE groups. (B) Differences in NRL distribution between VTE and non-VTE groups. (C) Differences in CRP distribution between VTE and non-VTE groups. (D) Differences in PCT distribution between VTE and non-VTE groups. \*indicates  $P < 0.05$ ; \*\*indicates  $P < 0.01$ .



**Figure 3** ROC curves of indicators with differences. **Notes:** (A) ROC curves of coagulation indicators. (B) ROC curves of inflammatory indicators.

**Table 4** Correlation Analysis of Coagulation and Inflammatory Indicators

	WBC		NLR		CRP		PCT	
	r	P	r	P	r	P	r	P
D-dimer	0.224	0.007*	0.202	0.016*	0.238	0.004*	0.023	0.793
TAT	0.190	0.022*	0.125	0.136	0.057	0.498	0.002	0.979
PIC	0.183	0.027*	0.148	0.075	0.109	0.190	0.012	0.888
tPAIC	0.143	0.086	0.103	0.219	-0.032	0.699	-0.021	0.807
TM	0.270	0.001*	0.429	<0.001*	0.162	0.049*	-0.016	0.857

Note: \*P<0.05.

As CRP is affected by immunosuppressive treatment, PCT was identified as a better marker than CRP for characterizing the level of inflammation. In addition, PCT has been found to be a reliable early marker for the differential diagnosis of pulmonary embolism and community-acquired pneumonia.<sup>21</sup> In our study, the AUC of PCT used for diagnosing VTE in pneumonia patients was also higher than that of CRP, which needs to be established in a large number of samples. The increase in CRP and PCT levels in the VTE group in our study indicated the existence of an increased inflammatory response in the process of thrombosis in patients with pneumonia.

TM is a transmembrane molecule secreted by endothelial cells. When the vascular endothelium is damaged, TM binds to thrombin and the complex activates protein C, changing from pro-coagulant and pro-inflammatory to anti-coagulant and anti-inflammatory.<sup>22,23</sup> Recombinant TM has been proven to be effective in treating sepsis caused by bacterial pneumonia by preventing excessive coagulation and regulating excessive inflammation.<sup>24</sup> Our study found that pneumonia patients with VTE had higher levels of TM, which may be a self-protection mechanism.

It is crucial to capture the initiation of the coagulation and fibrinolysis system. Unfortunately, thrombin and plasmin have a short half-life, making direct detection difficult. However, it was discovered that the complexes formed with antithrombin or antiplasmin, known as TAT and PIC, can be detected. Previous studies have analyzed the diagnostic and prognostic value of these two indicators of thrombotic and hemorrhagic disorders in patients with cancer, pediatric patients and postpartum women.<sup>25–28</sup>

Our research found that TAT and PIC were correlated with WBC count, indicating activation of both coagulation and inflammation in patients with pneumonia. t-PAIC is formed by plasminogen activator inhibitor-1 (PAI-1) and tissue plasminogen activator (tPA) at 1:1 concentration. An increase in t-PAIC levels indicates early activation of the fibrinolytic system and damage to endothelial cells. However, the reference interval of tPAI-C was different between male and female.<sup>12</sup> After PSM, we found that the level of t-PAIC in patients with VTE was higher than that in patients without VTE.

D-dimer is a biomarker for fibrin degradation that is released when a blood clot is formed and begins to break down. TAT can better capture the initial activation of the coagulation system in the early phase than D-dimer.<sup>29</sup> However, the ROC of D-dimer was higher in our study, which may be because the clots had already degraded during sample collection. Our data suggest that, with the exception of D-dimer, other coagulation and inflammatory indicators demonstrate relatively moderate diagnostic performance, with ROC values around 0.6, in identifying VTE in patients with pneumonia. However, further validation using a larger sample size is required to confirm these preliminary results.

We further investigated the correlation between the inflammatory and coagulation indicators in patients with pneumonia.

Correlation analysis revealed that D-dimer, TAT, PIC, and TM levels are associated with several inflammatory indicators. Specifically, TM correlated with WBC count, CRP level, and NLR. Therefore, TM may serve as an inflammatory immune factor that reflects the level of inflammation in patients with pneumonia.<sup>30</sup> The limitations of the study are the lack of long-term observation and evaluation as the patients compliance of follow-up after discharge is poor.

In summary, patients with pneumonia exhibit activation of both coagulation and fibrinolytic systems, accompanied by a significant increase in the level of systemic inflammatory responses. Coagulation indicators, such as TM, TAT, PIC, and D-dimer, can effectively monitor VTE formation in patients with pneumonia. In patients with pneumonia, the complex interplay between the coagulation and inflammatory pathways can exacerbate both processes, leading to increased

susceptibility to VTE. Monitoring these coagulation and inflammatory indicators can aid the early identification of high-risk individuals and inform clinical interventions to improve patient outcomes. Therefore, it is crucial to monitor coagulation indicators when inflammation indicators are elevated so that VTE can be detected early.

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## Disclosure

The authors declare that they have no competing interests in this work.

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